From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	09.03.2005

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
PU4962WO	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 03/39644	12.12.2003	13.12.2002

Applicant
SMITHKLINE BEECHAM CORPORATION et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PU4962WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US 03/39644	International filing date *(day/month/year)* 12.12.2003	Priority date *(day/month/year)* 13.12.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/46, A61K31/445, C07D451/04, A61P31/18		
Applicant SMITHKLINE BEECHAM CORPORATION et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.06.2004	09.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Seymour, L Telephone No. +49 89 2399-8694

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/39644

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-813 as originally filed

Claims, Numbers

1-61 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 42-53 with respect to industrial applicability; 1,2,4-23,25-61 (all part)

   because:

   ☒ the said international application, or the said claims Nos. 42-53 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1,2,4-23,25-61 (all part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	24
	No:	Claims	1-23, 25-61
Inventive step (IS)	Yes:	Claims	24
	No:	Claims	1-23, 25-61
Industrial applicability (IA)	Yes:	Claims	1-41, 54-61
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Claims 42-53 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

For reasoning with regards to unsearched subject-matter, see Form PCT/ISA/210 of the International Search Report. No international Preliminary Examination will be carried out with respect to subject-matter which is not covered by the search report (Rule 66.1(e) PCT).

Re Item IV

This International Searching Authority found multiple inventions in this international application, as follows:

1. Compounds of formula 1 according to claim 1 wherein the piperidine ring is not spiro fused and corresponding compositions and uses

2. Compounds of formula 1 according to claim 1 wherein the piperidine ring is spiro fused and corresponding compositions and uses

The problem underlying the present application is seen in the provision of further piperidine derivatives useful in the treatment of CCR5 mediated disorders, such as HIV infections.

The initial phase of the search revealed document D4 (see Item V) which discloses spiro fused antagonists of the chemokine receptor CCR5 falling within the scope of claim 1 (cf. "R1 and X taken together form a saturated, partially saturated or aromatic 5-7 membered ring having 0-3 heteroatoms chosen from oxygen, sulfur, nitrogen and phosphorus, that is fused to Ring A").

The requirement of Rule 13.2 PCT is thus not fulfilled in the present application since said prior art destroys the novelty of both the present common structure and activity. In other words, the structural feature that distinguishes the present compounds from those of said prior art differs in the above-mentioned groups i.e.

in group 1 the distinguishing feature lies the fact that position 4 of the piperidine ring is disubstituted and in group 2 in the nature of the substituents at the spiro-piperidine core structure. Starting from said prior art, the above-mentioned problem has thus been solved by different technical means, which are not so linked as to form a single general inventive concept (Rule 13.1 PCT).

Re Item V

1. Reference is made to the following documents:

D1: WO-A-99 04794 D2: WO-A-00 38680 D3: WO-A-02 079190
D4: WO-A-98 25605 D5: US-A-5 340 822 D6: BE-A-601 228
D7: US-A-2 773 870 D8: US-A-3 539 580 D9: US-A-3 334 106
D10: Archiv der Pharmazie, vol. 319, no. 319, 1986, p. 505-515, XP001085385
D11: J. Med. Chem. vol. 41, no. 23, 1998, p. 4623-4622, XP002173109
D12: US-A-2 248 018 D13: WO-A-98 25604 D14: JP-A-2002 348288

The opinion expressed below with regard to novelty, inventive step and industrial applicability refers only to subject-matter for which an international search report has been drawn up.

2. Novelty (Article 33(2) PCT)

2.1 The region of overlap with D1 can be regarded as a novel selection since this document does not disclose 4,4-disubstituted piperidines wherein one of the 4-substituents is -X-A as defined in present claim 1.

2.2 The compounds of D2 differ from the present compounds since piperidine is only disclosed as one of the potential terminal heterocycles on page 27, line 10.

2.3 The compounds of D3 differ from the present compounds in that the piperidine ring is not 4,4-disubstituted.

2.4 The compounds of D4, D13 and D14 disclose spiro fused antagonists of the chemokine receptor CCR5 falling within the scope of claim 1 (cf. invention 2).

2.5 The specific compounds disclosed in claim 24 are novel with respect to the prior art, but not the compounds of formula I as defined in claim 1 and claims dependent thereon (see reasoning for incomplete search for invention 1 and citations D5-D12 in search report). The pharmaceutical activities disclosed in said prior art partially overlap with those claimed (cf. specifically D5, column 1, lines 11-24 and e.g. claim 52).

3. Inventive step (Article 33(3) PCT)

The problem underlying the present application is seen in the provision of further piperidine derivatives useful in the treatment of CCR5 mediated disorders, such as HIV infections.

Invention 1

Documents D1 and D2 disclose CCR5 chemokine receptor antagonists useful in the treatment of HIV infections (see D1, claim 20 and p. 103, lines 12-17; D2, claims 5, 6). D3 discloses antagonists of the chemokine receptor MCP-1 also useful in the treatment of HIV infections (p. 12, lines 1-3).

The general formula of D1 overlaps with present formula I. The 4,4-disubstituted piperidine derivatives specifically disclosed in claim 15 of D1 differ from the present compounds only in the lack of terminal cycle A or in the lack of linker X (cf. e.g. D1, p. 206, 2nd compound). Given that only very minor modifications to the above compounds are required in order to arrive at the claimed derivatives, and the possibility of these modifications are suggested by D1, the present compounds in the breadth claimed in claims 1-23 must be regarded as an obvious solution to the above-mentioned problem.

For the present examples as claimed in claim 24, D2 could be regarded as being the closest prior art (cf. D2, claim 2), since the compounds disclosed therein differ from the compounds of D2 only in the definition of [Region α] (as defined in D2). There is no suggestion in D2 that this region could be replaced by 4-phenylpiperidin-4-yl moiety. The skilled person would not look to D1 when attempting to modify the compounds of D2 since in the former the terminal cyclic group (see definition of R^3) must be an aromatic group and may not be a tropane-like moiety. In D3 the piperidine moiety is not 4,4-substituted, so that this

document would also not lead to the present compounds. An inventive step can thus be acknowledged for claim 24.

Invention 2

Given that the compounds of D4, D13 and D14 have the same structure and activity as the present compounds of invention 2, the latter must be regarded as an obvious solution to the above-mentioned problem.

4. Industrial applicability (Article 33(4) PCT)

For the assessment of the present claims 42-53 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.